Bisphenol A Effects on Gonadotroph Function

Bisphenol A effects on gonadotroph function: disruption of pituitary cell-cell communication?

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Since the publication of a joint International Programme on Chemical Safety report in 2002 assessing the scientific knowledge of endocrine disruptors, there has been a dramatic increase in both awareness of the risk they may pose and studies of potential health implications for humans and wildlife (1). Of all the endocrine disruptors studied to date, there has been considerable focus on bisphenol A (BPA), in particular on its effects on the reproductive axis (2). BPA is a widely used industrial chemical which has been found in 95% of urine samples from adults the United States (3), with contaminated food and water accounting for 90% of exposure (4). Whilst most studies have focused on the estrogenic activity of BPA, it has also been shown to bind to androgen and thyroid hormone receptors, suggesting that it may disrupt multiple endocrine systems. In the reproductive axis, BPA has been reported to adversely affect several end points of fertility, advance puberty and induce polycystic ovarian syndrome (2).

In this edition of Endocrinology, Eckstrum and colleagues (5) describe effects of BPA on gonadotrophs during an important pituitary developmental window in neonatal mice. The authors have found that the gene encoding intracellular adhesion molecule-5 (*Icam5*; also known as telencephalin) is more highly expressed in the pituitary of day-old female mice compared with their male littermates. They go on to show that the RNA and protein is predominantly expressed in gonadotrophs, with increased expression during the early postnatal period (up to day 20), with a continued higher expression in females than males. The disrupting effect of BPA on this expression is demonstrated in females and males in *ex vivo* cultures, and in females *in vivo,* with lower expression of *Icam5.* This work builds on previous studies describing effects on BPA exposure *in utero* by the same group, where different effects on the reproductive axis were described, consistent with the concept that specific windows of the development of endocrine axes may be differentially affected by the same endocrine disruptor.

What is the potential role of Icam5 in normal pituitary function? Expression of this gene has previously been considered to occur only in the telencephalon, where it has a role in the regulation of the interactions between axonal protrusions and dendritic spines which form neuronal synapses. Loss of *Icam5* in knockout mice leads to a reduction in filopodia which develop into dendritic spines (6) and increased spinal maturation, overexpression the reverse. This kind of cell-cell interaction leading to functional connectivity has been described in the pituitary, where homotypic cell networks have been shown to exist, with important roles in the regulation of cell function at both the level of secretion (7) and gene expression (8). The proteins regulating this cell network formation have not been identified but those with a function similar to that described for ICAM5 are likely to be mediators, making it a likely candidate. In the neonate, it is possible that ICAM5 mediates the formation of the gonadotroph network described by Budry and colleagues (9). This network begins its development before birth and it would be interesting to determine whether there is a window of *Icam5* expression in these early gonadotrophs. In the adult, ICAM5 was only found in a subset of gonadotrophs- what could be its role at this time? There is considerable plasticity in the organisation of pituitary cell networks, dependent on physiological status and we would suggest that *Icam5* may have a role in

reorganisation of the gonadotroph network. Interestingly, gonadotroph protrusions, similar to the filopodia described in telencephalic neurons, have been described in adult female mice, with a potential role in remodelling the relationship of the gonadotroph network with the vasculature (10). Again, there is clear potential for a role for *Icam5* in mediating this remodelling.

What are the potential consequences of disrupting *Icam5*? Loss of Icam5 may be expected to lead to disruption of normal reproductive function through a failure of normal gonadotroph network formation, with potential alteration of secretory and gene transcriptional responses to GnRH. There are no reports in the literature of a reproductive phenotype in mice with a loss of functional ICAM5 but it is possible that subtle effects, such as altered vaginal opening or disrupted estrous cycles may not have been noted, especially in studies where the purpose of generating the knockout mouse was focused on other expected phenotypes. A reduced expression of *Icam5* following neonatal exposure to BPA may be expected to have a similar effect. It should be noted that, whilst there is controversy over the levels of exposure of BPA that may cause endocrine disruption, the doses affecting *Icam5* expression in *ex vivo* cultures in the study of Eckstrum and colleagues (5) are only 10 fold higher than the US Environmental Protection Agency estimates of a safe dose for oral exposure.

It is clear that further studies of the role of *Icam5* in normal pituitary function are warranted. In particular, it would be interesting to determine whether the reduction in *Icam5* resulting from neonatal exposure to BPA, or from loss of functional ICAM5, translates into an altered function of the adult gland and an impact on reproductive function through disrupted gonadotroph networks. This would have implications for a potential impact of endocrine disruptors on other pituitary networks, with far-reaching consequences for physiological regulation and health.

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